

Risk Factors of Gastrointestinal Stromal Tumor Recurrence

Gastrointestinal Stromal Tümör Rekürrensinde Risk Faktörleri

Abstract

Aim: Gastrointestinal stromal tumors (GIST) are the most common mesenchymal neoplasia of gastrointestinal system. Radical surgery with negative margin is the most important step for treatment of GIST. The primary aim of this study was to evaluate the risk factors for recurrence in patients who underwent surgery with diagnosis of GIST. Secondary aim was to reveal the factors that affect survival.

Materials and Methods: The data of 28 GIST patients who underwent surgery in our clinic between January 2013 and August 2019 were analyzed retrospectively. Patients preoperative radiological images, histopathological and immunohistochemical findings were noted.

Results: Eighteen patients were male, and ten patients were female. Median age was 64.5 (range: 50-87). Twenty-six patients (92.2%) underwent open surgery and 2 patients (7.1%) underwent laparoscopic surgery. Fifteen (53.6%) of the 28 tumors were located in the stomach, 10 (35.7%) in the small intestine, 2 (7.1%) in the duodenum and 1 (3.6%) was located multifocal. Mean tumor diameter was 10.1 cm (range: 0.5-21). The number of patients with recurrence was 5 (17.9%). Tumor with necrosis, tumor located in an organ other than the stomach, and the high number of tumor mitosis revealed a significant difference for recurrence. In addition, large tumor size revealed significant statistical difference for recurrence. The median follow-up period was 26 (3-60) months. Necrosis of tumor and tumor type were the factors that significantly shortened survival.

Conclusion: In this study which we examined the GIST recurrence, it was observed that tumor size, tumor necrosis, increased number of mitosis and tumors located in an organ other than stomach are risk factors for recurrence. In this study which we examined GIST recurrence, tumor size, tumor necrosis, increased number of mitoses and tumors located in an organ other than the stomach are found to be risk factors for recurrence.

It was observed that the factors affecting the survival times, which are the secondary aim of the study, were cell type and tumor necrosis.

Keywords: Gastrointestinal stromal tumor; gastrointestinal system; mesenchymal cancer; surgery

Öz

Amaç: Gastrointestinal stromal tümörler (GIST), gastrointestinal sistemin en yaygın mezenkimal neoplazilerindedir. Temiz sınırlı cerrahi rezeksiyon GIST tedavisinin en önemli basamaklarından birini oluşturmaktadır. Bu çalışmada primer amaç GIST tanısıyla ameliyat ettiğimiz hastalarda rekürrens için risk faktörlerini değerlendirmek, sekonder amaç ise hangi faktörlerin sağkalıma etki ettiğini ortaya koymaktır.

Gereç ve Yöntemler: Ocak 2013 ile Ağustos 2019 tarihleri arasında kliniğimizde cerrahi olarak tedavi edilen 28 GIST vakasının verileri retrospektif olarak incelendi. Hastalar operasyon öncesi görüntülemeler, histopatolojik ve immünohistokimyasal yönünden incelendi ve hasta bilgileri dokümanete edildi.

Bulgular: Hastaların 18'i erkek, 10'u kadındı. Medyan yaş 64,5 idi. (en genç 50, en yaşlı 87). Hastaların 26'sı (%92,9) konvansiyonel, 2'si (%7,1) laparoskopik yöntemle ameliyat edildi. Hastaların 15'inde (%53,6) lezyon midede, 10'ununda (%35,7) jejunum-ileumda, 2'sinde (%7,1) duodenumda, 1'inde (%3,6) ise multifokalda yerleşmişti. Ortalama tümör çapı 10,1cm idi (En uzun çap 21 cm, en kısa çap 0,5 cm). Hastaların 27'sinde (%96,4) DOG-1, 24'ünde (%85,7) CD117, 23'ünde (%82,1) CD-34, 9'unda (%32,1) SMA, 3'ünde (%10,7) Desmin, 2'sinde (%7,1) S-100 pozitifliği izlendi. Toplam rekürrens görülen hasta sayısı 5 idi (%17,9). Yapılan istatistiksel analizler sonucunda tümörde nekroz olması, tümörün mide dışında bir organda yerleşmiş olması ve tümör mitoz sayısının yüksek olması rekürrens için anlamlı istatistiksel fark ortaya çıkarmıştır. Ayrıca tümör boyutunun büyük olması rekürrens için anlamlı istatistiksel farklılık ortaya çıkarmıştır. Medyan takip süresi 26 (3-60) ay idi. Yapılan analizlerde tümörde nekroz görülmesi ve tümörün iğsi hücreli tipte olması sağkalımı anlamlı ölçüde kısaltan etkenlerdi.

Sonuç: GIST rekürrensini incelediğimiz bu çalışmada tümör boyutunun büyük olması, tümör nekrozu, mitoz sayısının artmış olması ve tümörün mide dışında bir organda yerleşmiş olması rekürrens için risk faktörü olduğu gözlemlenmiştir. Çalışmanın sekonder amacı olan sağkalım sürelerini etkileyen faktörlerin ise hücre tipi ve tümör nekrozu olduğu görülmüştür.

Anahtar Sözcükler: Gastrointestinal stromal tümör; gastrointestinal sistem; mezenkimal kanser; cerrahi

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INTRODUCTION

Gastrointestinal stromal tumors (GIST) are the most common mesenchymal neoplasia of gastrointestinal system (1). GISTs develop from Cajal cells in the wall of the gastrointestinal tract (2). C-kit overexpression and platelet-induced growth factor alpha receptor (PDGFR Alpha) mutation have an important role in GIST pathogenesis (3). When the demographic distribution is analyzed, GISTs generally occurs in middle-aged adults (2). GISTs are most commonly located in the stomach (60-70%), small intestine (20-30%), colon (10%) and esophagus, respectively (4). Approximately 10-30% of GISTs have malignant potential (5). GISTs rarely cause lymph node or extra abdominal organ metastasis (6).

Eighty percent of primary GISTs occur with symptoms like hemorrhage, obstruction and gastric pain. About twenty percent of the patients are asymptomatic and diagnosing incidentally (7).

In the pre-treatment evaluation, upper gastrointestinal system endoscopy and abdominal CT can be used as the first option (8). Endoscopic biopsy may result negative because of the mass develops from the muscular layer of the stomach. EUS-guided or percutaneous techniques are recommended to obtain adequate biopsy materials (8,9).

The first approach in GISTs treatment should be resection of the tumor with negative margin (9,10). Avoiding rupture during resection is important to prevent intraabdominal spread (9). Enucleation is not recommended because recurrence of GIST occurs more frequently in patients who underwent enucleation (9). Tyrosine-kinase inhibitors are the first choice for treatment of inoperable locally advanced and/or metastatic disease (11). In the case of metastatic disease, surgery is not the first-line treatment alternative, but it can be performed in mandatory situations like bleeding and obstruction. Adjuvant therapy is recommended for high-risk patients after R0 surgical resection (8,11).

Although the combination of R0 surgical resection and adjuvant therapy generally provides adequate cure, recurrence may occur in some patients. Recurrences are frequently observed locally, in the liver or on the peritoneal faces (8,11,12). The primary aim of this study was to evaluate the risk factors for recurrence in patients who underwent surgery with diagnosis of GIST. Secondary aim was to reveal the factors that affect survival.

MATERIALS AND METHODS

The data of 28 GIST patients who underwent surgery in Istanbul Medeniyet University Goztepe Education and Research Hospital, General Surgery Clinic between January 2013 and August 2019 were analyzed retrospectively. This study was approved by Istanbul Medeniyet University Goztepe Training and Research Hospital Clinical Research Ethics Committee (Reference Number: 2019/0535). Wedge resection of the tumor with linear stapler was the surgical technique used in both open and laparoscopic surgeries. No additional procedures such as lymph node dissection or metastasectomy were performed. Each patient's age, gender, operation date, preoperative radiological findings, tumor resection margins, tumor size, histological type, mitosis count, growth pattern, necrosis, GIST risk group, imatinib therapy, CD117, DOG-1, CD34, SMA, S-100, Desmin, Ki-67 and survival data were recorded. The data were documented through our hospital system 'Nucleus'. Patients under 18 years old, with residual tumor and without follow-up data were excluded from the study. Recurrence was defined as local recurrence or metastasis during follow-up. All variables were analyzed statistically to be evaluated in terms of the relationship between recurrence or mortality. Variables were analyzed statistically, taking into account their number and proportional values, because some variables were too few in number. The data were analyzed by using IBM SPSS 23. Categorical data were analyzed by chi-square and continuous data by t-test. Survival data were analyzed by using the Kaplan-Meier method. The p-value<0,05 was considered statistically significant.

RESULTS

A total of 28 patients met the inclusion criteria. Includes patients demographic and histopathological examination data (Table 1). Eighteen patients were male and 10 were female. The median age was 64.5 (50-87). The median follow-up period was 26 (3-60) months. Twenty-six patients (92.2%) underwent open surgery and 2 patients (7.1%) underwent laparoscopic surgery. Fifteen (53.6%) of the 28 tumors were located in the stomach, 10 (35.7%) in the small intestine, 2 (7.1%) in the duodenum and 1 (3.6%) was located multifocal. Histopathological examination was re-

Table 1. Patients demographic and histopathological examination data

	Value
Age(Median)	64.5(50-83)
Gender	
Male	18 (64.3%)
Female	10 (35.7%)
Tumor Location	
Stomach	15(53.6%)
Ileum-Jejenum	10(35.7%)
Duodenum	2(7.1%)
Multifocal	1(3.6%)
Type of tumor	
Spindle	22(78.6%)
Mixt	5(17.9%)
Epithelioid	1(3.6%)
Necrosis of tumor	
Tumor with necrosis	8(28.6%)
Tumor without necrosis	20(71.4%)
Risk Group	
0	4(14.3%)
1	11(39.3%)
2	4(14.3%)
3	9(32.1%)
CD117	
Positive	24(85.7%)
Negative	4(14.3%)
DOG1	
Positive	27(96.4%)
Negative	1(3.6%)
CD34	
Positive	23(82.1%)
Negative	5(17.9%)
SMA	
Positive	9(32.1%)
Negative	19(67.9%)
S100	
Positive	2(7.1%)
Negative	26(92.9%)
Desmin	
Positive	3(10.7%)
Negative	25(89.3%)
Resection Margin	
Negative	25(89.3%)
Positive	3(10.7%)

	Value
Growth Pattern	
Expansive	25(89.3%)
Infiltrating	3(10.7%)
Surgical Technique	
Open	26(92.9%)
Laparoscopic	2(7.1%)
Tyrosine Kinase Inhibitor Treatment	
Yes	7(25%)
No	21(75%)

tissue. Mean tumor diameter was 10.1 cm (0.5-21). Immunohistochemical examination revealed positive expression of DOG-1 in 27 (96.4%), CD117 expression in 24 (85.7%), CD-34 expression in 23 (82.1%), SMA expression in 9 (32.1%), Desmin expression in 3 (10.7%) and S-100 expression in 2 (7.1%) cases. The number of patients with recurrence was 5 (17.9%). During post-operative follow-ups, metastasis occurred in 4 (14.3%) cases and local recurrence occurred in 2 (7.1%) cases. One of the patients had each of metastasis and local recurrence. The number of patients with recurrence was 5 (17.9%).

In the statistical analysis for the recurrence development, which is the primary aim of the study, the analysis of the effect of categorical data on recurrence is presented (Table 2). Analysis of the effect of numerical data on recurrence is presented (Table 3). Non-gastric location of tumor (p=0.013) and tumor with necrosis (p=0.015) significantly increased recurrence. In the analysis of tumor diameter, the mean diameter of the tumor was 14.9 cm in patients with recurrence, and 7.8 cm in patients without recurrence. In the analysis of the effect of this data on recurrence, it was observed that the large tumor diameter increased recurrence (p=0.016). In addition, the increased number of tumor mitosis was found to significantly increased recurrence (p=0.004). There were no significant findings effect on recurrence were analyzed.

To assess the secondary aim of the study, variables effect on survival was analyzed. During follow-up, a total of 6 (21.4%) patients resulted in mortality. Estimated mean survival in all patients was 47.6 months (Figure 1). In the statistical analysis, patients with mixed type of tumor (p=0.04) or tumor with necrosis (p=0.03) had significant shortener survival.

vealed to the resection materials, tumor types reported as 22 spindles cells (78.6%), 5 mixed (17.9%) and 1 epithelioid (3.6%). Twenty-five (89.3%) of the resected tumors had negative margins, 3 (10.7%) of them had penetration of the tumor cells into the surrounding

Table 2. Analysis of the effect of categorical data on recurrence

	Patients with Recurrence	Patients without recurrence	P
Gender			0.601
Male	3(16.7%)	15(83.3%)	
Female	2(20.0%)	8(80.0%)	
Tumor Location			0.013
Stomach	0(0%)	15(100%)	
Other	5(38.5%)	8(61.5%)	
Type of tumor			0.285
Spindle	3(13.6%)	19(86.4%)	
Other	2(33.3%)	4(66.7%)	
Necrosis of tumor			0.015
Tumor with necrosis	4(50%)	4(50%)	
Tumor without necrosis	1(5%)	19(95.0%)	
Risk Group			0.066
0	0(0%)	4(100%)	
1	1(9.1%)	10(90.9%)	
2	0(0%)	4(100%)	
3	4(44.4%)	5(55.6%)	
CD117			0.617
Positive	4(16.7%)	20(82.3%)	
Negative	1(25.0%)	3(75%)	
DOG1			0.179
Positive	4(14.8%)	23(85.2%)	
Negative	1(100%)	0(0%)	
CD34			0.658
Positive	4(17.5%)	19(82.6%)	
Negative	1(20%)	4(80%)	
SMA			0.527
Positive	2(22.2%)	7(77.8%)	
Negative	3(67.9%)	16(32.1%)	
S100			0.331
Positive	1(50%)	1(50%)	
Negative	4(15.4%)	22(84.6%)	
Desmin			0.459
Positive	1(33.3%)	2(66.7%)	
Negative	4(16%)	21(84%)	
Resection Margin			0.459
Negative	4(16%)	21(84%)	
Positive	1(33.3%)	2(66.7%)	

	Patients with recurrence	Patients without recurrence	P
Growth Pattern			0.073
Expansive	3(12.0%)	22(88.0%)	
Infiltrating	2(66.7%)	1(33.0%)	
Surgical Technique			0.669
Open	5(19.1%)	21(80.8%)	
Laparoscopic	0(0%)	2(100%)	
Tyrosine Kinase Inhibitor Treatment			0.281
Yes	0(0%)	8(100%)	
No	5(25%)	15(75%)	

develop before or after surgical removal of the tumors. Aim of this study was to evaluate the risk factors for recurrence in patients who underwent surgery with diagnosis of GIST. Secondary aim was to reveal the factors that affect survival.

The National Cancer Institute (NIH) evaluated the risk factors in GIST recurrence and established a consensus by study of Fletcher et al. in 2002 (13). According to this study, tumor location, tumor size and the number of mitosis more than 50 were risk factors for tumor recurrence. In our study, it was observed that tumor location, size and number of mitosis increased recurrence.

In the GIST study conducted by De Matteo et al. with 200 patients in 2000, there was a 30% recurrence rate at 2-year follow-up. Most common recurrence sites in this study were tumor resection area and liver (14). In our study, the recurrence rate was 17.9% and these recurrences were located in tumor resection area and liver. Despite the similarity of recurrence location, our recurrence rate is less than this study because treatment modalities have progressed in the past time.

A meta-analysis by Yi et al. on the effect of necrosis on GIST prognosis in 2019 included 18 studies with 2320 patients (15). This meta-analysis showed negative effect of necrosis on disease-free survival, survival without recurrence and overall survival. Our study also revealed significant relation between necrosis and recurrence but unlike the meta-analysis no relation between necrosis and survival was detected.

Seagles-Rojas et al. conducted a study to investigate the effect of Ki-67 index on GIST recurrence with 43 patients in 2018. In this study, Ki-67 had no effect on recurrence, but male gender and tumor size had ef-

DISCUSSION

GISTs are the most commonly operated mesenchymal tumors of the gastrointestinal system. Although stomach is the most common location site, GISTs may located in other organs too. Most of the GIST patients have benign clinical course but metastatic disease can

Table 3. Analysis of the effect of numerical data on recurrence

	Average in patients with GIST Recurrence (n=5)	Average in Patients without GIST recurrence (n=23)	p
Age	67.4±9.1	66.1±10.8	0.794
Tumor Diameter (cm)	14.9±3.4	7.8±5.8	0.016
Ki67 index	17.3	13.9	0.349
Number of Mitosis (50 magnification)	47	3	0.004

fect on recurrence (16). Like this study we found that Ki-67 have no relation with recurrence. In addition, although we obtained results in parallel with this study in tumor size, we could not find a significant difference in gender.

In the study of Atak et al. the data of 21 GIST patients were evaluated retrospectively, the lesion was most frequently located in the stomach with 76.1%, followed by the small intestine (17). In our study, the distribution of tumor location was similar, and tumor was most frequently located in stomach (53.4%) and small intestine (35%) respectively.

In a study conducted by Mazer et al. in 2019 to evaluate minimally invasive resection in 77 GIST patients, 53 (68%) patients underwent laparoscopic resection. Postoperative hospital stay was shorter and complication rates were lower in laparoscopic resection. In ad-

dition, there were 5 (6%) patients with recurrence (18). In our study, 2 (7.1%) patients underwent laparoscopic resection, and our recurrence rate was 18%. Laparoscopy is proven to safe for GIST surgery, and it may be beneficial to increase minimally invasive resections and improve patient outcomes in eligible patients.

This study has some limitations. The sample size of the study, which is primarily a single-center retrospective study, is the most important limitation. In addition, the relatively short follow-up period prevents the long-term evaluation of survival, the secondary endpoint of the study.

CONCLUSION

In conclusion, we observed that tumor size, tumor necrosis, increased number of mitosis and tumors located in an organ other than stomach

are risk factors for recurrence. It was observed that the factors affecting the survival times, which are the secondary aim of the study, were cell type and tumor necrosis. For expand the analysis of factors affecting survival, it will be appropriate to conduct studies with longer follow-up.

Conflict of Interest and Financial Disclosure

The authors declare that they have no conflict of interest to disclose. The authors also declare that they did not receive any financial support for the study.

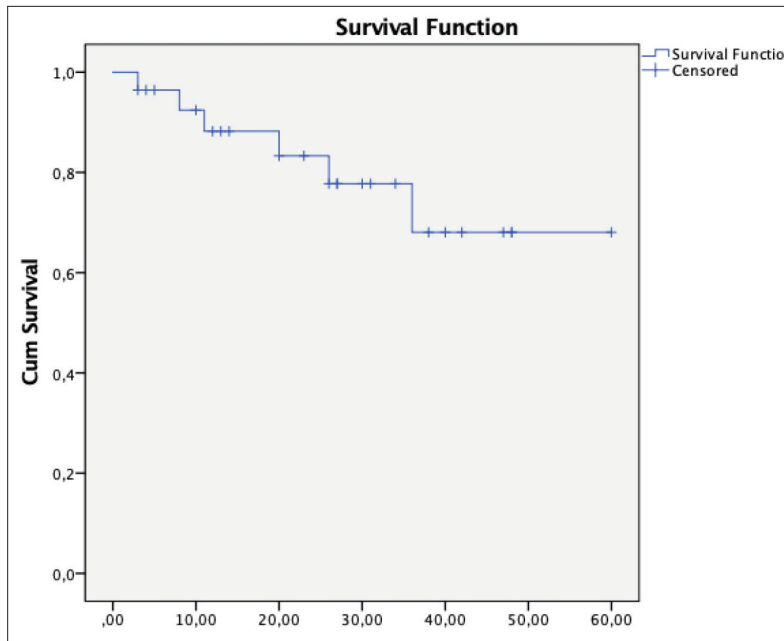


Figure 1. Total survival in all patients (Month)

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